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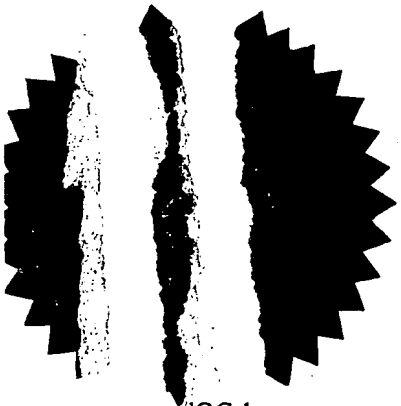

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PATENTS ACT 1977

25 OCT 1985

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PATENTS FORM No. 1/77 (Revised 1982)

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The Comptroller
The Patent Office
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London, WC2A 1AY

1985
26407

REQUEST FOR GRANT OF A PATENT

8526407

THE GRANT OF A PATENT IS REQUESTED BY THE UNDERSIGNED ON THE BASIS OF THE PRESENT APPLICATION

I Applicant's or Agent's Reference *(Please insert if available)* JB/B1942

II Title of Invention NOVEL COMPOUNDS

III Applicant or Applicants *(See note 2)*

Name (First or only applicant) Beecham Group p.l.c.

Country United Kingdom State ADP Code No.

Address Beecham House, Great West Road, Brentford TW8 9BD
Middlesex, England

Name (of second applicant, if more than one)

Country State

Address

IV Inventor (see note 3)

(a) The applicant(s) is/are the sole/joint inventor(s) or
(b) A statement on Patents Form No 7/77 is/will be furnished

V Name of Agent (if any) *(See note 4)* J.H.F. Blake ADP CODE NO

VI Address for Service (See note 5)
Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road
Epsom, Surrey KT18 5XQ England

VII Declaration of Priority (See note 6)

Country	Filing date	File number

VIII The Application claims an earlier date under Section 8(3), 12(6), 15(4), or 37(4) (See note 7)

Earlier application or patent number and filing date

IX Check List (*To be filled in by applicant or agent*)

A The application contains the following number of sheet(s)		B The application as filed is accompanied by:-	
1 Request	1 Sheet(s)	1 Priority document	
2 Description	11 Sheet(s)	2 Translation of priority document	
3 Claim(s)	Sheet(s)	3 Request for Search	
4 Drawing(s)	6 Sheet(s)	4 Statement of Inventorship and Right to Grant	
5 Abstract	Sheet(s)		

X It is suggested that Figure No ..... of the drawings (if any) should accompany the abstract when published.

XI Signature (*See note 8*) J.H.F. Blake Chartered Patent Agent
Agent for the Applicants

NOTES:

1. This form, when completed, should be brought or sent to the Patent Office together with the prescribed fee and two copies of the description of the invention, and of any drawings.
2. Enter the name and address of each applicant. Names of individuals should be indicated in full and the surname or family name should be underlined. The names of all partners in a firm must be given in full. Bodies corporate should be designated by their corporate name and the country of incorporation and, where appropriate, the state of incorporation within that country should be entered where provided. Full corporate details, eg "a corporation organised and existing under the laws of the State of Delaware, United States of America," trading styles, eg "trading as xyz company", nationality, and former names, eg "formerly [known as] ABC Ltd." are not required and should not be given. Also enter applicant(s) ADP Code No. (if known).
3. Where the applicant or applicants is/are the sole inventor or the joint inventors, the declaration (a) to that effect at IV should be completed, and the alternative statement (b) deleted. If, however, this is not the case the declaration (a) should be struck out and a statement will then be required to be filed upon Patent Form No 7/77.
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6. The declaraton of priority at VII should state the date of the previous filing and the country in which it was made and indicate the file number, if available.
7. When an application is made by virtue of section 8(3), 12(6), 15(4) the appropriate section should be identified at VIII and the number of the earlier application or any patent granted thereon identified.
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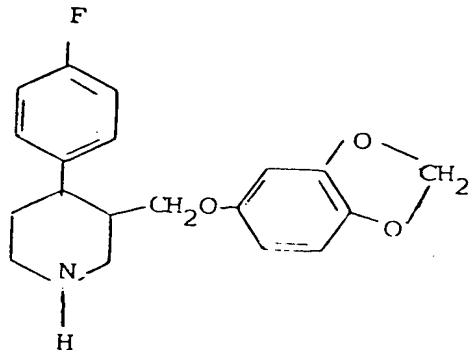
(6649) Dd 8818957 50M 5/84 SP&D Gp 606

B1942

NOVEL COMPOUNDS

This invention relates to crystalline paroxetine hydrochloride, its preparation and its use as a therapeutic agent.

US Patent 4007196 discloses a class of compounds that are inhibitors of 5-hydroxytryptamine (5HT) uptake and thus of therapeutic use as anti-depressants. In Example 2 of the US patent there is described the preparation of (-)-trans-4-(4'-fluorophenyl) 3-(3'4'-methylenedioxyphenoxymethyl)-piperidine of formula I:



(I)

In this specification the compound of formula I is referred to by its generic name of paroxetine.

Because of its basicity, it is preferred that paroxetine is used as a therapeutic agent in the form of an acid addition salt. In Example 2 of US Patent 4007196, paroxetine is obtained as the free base and then converted to its maleic acid salt.

The acetate salt of paroxetine has been used in most of the published experimental trials [for example, Psychopharmacology, 57, 151-153 (1978); bid. 68, 229-233 (1980); and European Journal of Pharmacology, 47 (1978) 351-358]. There has also been limited use of the hydrochloride salt (in aqueous solution) [Acta. Pharmacol. et Toxicol. 1979, 44, 289-295]. However, the preparation of paroxetine hydrochloride has not been described in the literature.

In general, the hydrochloride salt of a basic compound is preferred for therapeutic use because of its physiological acceptability.

However for commercial use it is also important that the solid product should have good handling qualities.

We have found that amorphous paroxetine hydrochloride is a hygroscopic solid of poor handling qualities.

It has now been discovered that paroxetine hydrochloride can be produced in crystalline form in a manner reproducible on a commercial scale.

Accordingly the present invention provides crystalline paroxetine hydrochloride as a novel material, in particular in pharmaceutically acceptable form.

It has been discovered that crystalline paroxetine hydrochloride can exist in at least two different pseudo-polymorphic forms,

1) a hemihydrate
2) an anhydrate

It has also been discovered that paroxetine hydrochloride can form crystalline solvates with certain solvents such as certain lower alcohols and acetone, in particular isopropyl alcohol.

Accordingly the present invention provides as novel forms of crystalline paroxetine hydrochloride:

1) paroxetine hydrochloride hemihydrate
2) paroxetine hydrochloride anhydrate
3) paroxetine hydrochloride isopropanol solvate

Paroxetine hydrochloride hemihydrate normally has a melting point in the range of 128 - 132°C, preferably 129 - 131°C. It is stable and non-hygroscopic. It is characterised by an X-ray powder diffractogram as shown in the accompanying drawing (Fig.1). A typical Nujol infra-red spectrum (Fig.2) and DSC profile (Fig.3) is also shown. Under extreme dessication conditions the bound water may be removed to give the pseudopolymorphic anhydrate form, but on rehydration it rapidly reforms the hemihydrate.

Paroxetine hydrochloride anhydrate has a melting point in the range of 115 - 119°C, preferably 116 - 118°C. It is hygroscopic. It is characterised by an X-ray powder diffractogram as shown in the accompanying drawing (Fig.4). A typical Nujol infra-red spectrum (Fig.5) and DSC profile (Fig.6) is also shown. Water is easily lost on heating and the product contains a variable amount of 'free' water depending on drying and storage conditions. Under normal ambient conditions it contains approx 2 to 4% by weight of water.

Paroxetine hydrochloride isopropanol solvate has a melting point in the range of 97 - 102°C. It appears to have the structure of the anhydrate pseudopolymorphic form by consideration of its infra-red spectrum. The solvent is fairly weakly bound and may be removed by heating under vacuum. The solvate contains approx. 1 mole of isopropanol per mole.

The existence of 2 distinct forms is confirmed by the distinctive X-ray powder diffractograms, infra-red spectra and the separated melting points. Differential scanning calorimetry of the two forms in sealed pans gives distinct profiles which are consistent with the observed melting point differences. These techniques may also be used to characterize product form.

The present invention also provides a process for producing crystalline paroxetine hydrochloride which comprises forming a solution of paroxetine hydrochloride and precipitating the crystalline form from solution.

The solution may be formed by dissolution of pre-formed paroxetine hydrochloride or by forming the hydrochloride in situ. The hydrochloride may be formed from a solution of paroxetine free base or a salt other than the hydrochloride by contacting it with hydrogen chloride.
For example a solution of hydrogen chloride, for example concentrated hydrochloric acid or an organic solvent saturated with hydrogen chloride may be added to a solution of paroxetine salt. Alternatively hydrogen chloride gas may be passed through the paroxetine (salt) solution.

Paroxetine base may be prepared by the procedure disclosed in US Patent 4007196. The US Patent also gives procedures for preparing salts of paroxetine with various organic acids.
Typically, paroxetine hydrochloride may be obtained from an organic solution e.g. in toluene, of the free base by adding an appropiate amount of aqueous HCL.

In a procedure using a salt, paroxetine hydrochloride may be produced from paroxetine acetate. The acetate may be obtained by reaction of acetic acid and paroxetine base in a non-polar solvent, such as diethyl ether or isopropyl ether. Alternatively it may be obtained from an aqueous solution obtained by extraction from a water-immiscible solvent eg. toluene, ethyl acetate, by the addition of water and an appropriate amount of acetic aid.

Before conversion to the hydrochloride or crystallisation it may be desirable to remove impurities, by conventional purification techniques, since it has been found that some impurities may act as crystallisation inhibitors.

The crystalline anhydrate form of paroxetine hydrochloride may be prepared via the initial formation of a crystalline solvate e.g. propan-2-ol or acetone solvate, of the hydrochloride and followed by the removal of the solvating solvent. The IPA solvate may be conveniently obtained by crystallisation from propan-2-ol, ideally under anhydrous conditions, by adding gaseous or concentrated hydrochloric acid to a solution of the free base or acetate salt in propan-2-ol, or by crystallising or recrystallising preformed paroxetine hydrochloride from propan-2-ol solution. The solvent of solvation may be removed by

drying, typically under vacuum at high temperature e.g. 60°C, to give the hygroscopic anhydrate.

Paroxetine hydrochloride may be obtained as a crystalline hemihydrate by crystallization after addition of an aqueous solution of hydrochloric acid to a solution of paroxetine free base in water immiscible solvents e.g. toluene, or by crystallisation from water miscible solvents which do not form a solvate (e.g. IMS) after adding aqueous hydrochloric acid to a solution of the free base or by crystallising or recrystallising paroxetine hydrochloride from a solvent system containing water e.g. IMS/water. Alternatively the hydrochloride hemihydrate can be produced via anotherparoxetine salt by the addition of hydrochloric acid to an aqueous solution of the salt e.g. acetate.

In practice, the earlier described procedure for producing the anhydrate may result in the formation of some hemihydrate. The proportion of anhydrate to hemihydrate can be increased by drying at elevated temperatures. The procedure for producing the hemihydrate will normally result in formation of hemihydrate free from contamination by anhydrate.

In a preferred aspect, this invention provides paroxetine hydrochloride hemihydrate which is substantially free from anhydrate, and paroxetine chloride anhydrate substantially free from hemihydrate. However the present invention includes within its scope mixtures which contain a major proportion of either of these two forms.

To obtain the anhydrate by crystallisation/recrystallisation, the solvent of choice is anhydrous isopropanol.

The hemihydrate can be obtained by crystallisation from a range of solvents, although seeding may be necessary in some instances, after addition of aqueous HCl to a solution of the free base or another salt . Solvents which have been found suitable are toluene, water, IMS, lower alcohols and ethyl acetate. The same solvent range may be used for recrystallizatation.

In its preferred aspect the present invention provides paroxetine hydrochloride hemihydrate and paroxetine hydrochloride anhydrate in pharmaceutically acceptable form.

The present invention also provides a pharmaceutical composition comprising crystalline paroxetine hydrochloride, especially the hemihydrate or anhydrate, and a pharmaceutically acceptable carrier.

The compositions of this invention are usually adapted for oral administration, but formulations for dissolution for parenteral administration are also within the scope of this invention.

The composition is usually presented as a unit dose composition containing from 1 to 200 mg, more usually from 5 to 100 mg, for example 10 to 50 mg such as 12.5, 15, 20, 25 or 30 mg. Such composition is normally taken from 1 to 6 times daily, for example 2, 3 or 4 times daily so that the total amount of active agent administered is within the range 5 to 400 mg.

Preferred unit dosage forms include tablets or capsules.

The composition of this invention may be formulated by conventional methods of admixture such as blending, filling and compressing.

Suitable carriers for use in this invention include a diluent, a binder, a disintegrant, a colouring agent, a flavouring agent and/or a preservative. These agents may be utilized in conventional manner, for example in a manner similar to that already used for clinically used anti-depressant agents.

The invention also provides a method of treatment of depression in mammals including humans which method comprises administering an effective amount of pharmaceutically acceptable crystalline paroxetine hydrochloride.

The invention further provides pharmaceutically acceptable crystalline paroxetine hydrochloride for use in the treatment of depression.

The following Examples illustrate the invention.

Example 1

(-)Trans-4-(4'-fluorophenyl)-3-(3'4'-methylenedioxy-phenoxymethyl)piperidine hydrochloride (paroxetine hydrochloride) as anhydrate

Crude paroxetine free base (0.341 kg) was dissolved in diethyl ether (3.5 litres) and stirred with aluminium oxide (ca.0.3 kg) for about 3 hours. Charcoal (15 g) and filter aid (celite, 15 g) were added and the mixture filtered through a layer of aluminium oxide, the filtered solids being washed with more ether. To the combined ether solutions was added a mixture of acetic acid (66 ml) and ether whereupon the acetate of paroxetine crystallised and was filtered off, washed with ether and dried.

The acetate salt was dissolved in isopropanol (2.4 litres) and treated with a mixture of concentrated hydrochloric acid (75 ml) and more isopropanol. After standing at 0°C for about 16 hours, the crystals of the hydrochloride salt containing isopropanol were filtered off and dried. The salt was stirred in distilled water (0.5 litres) for about 20 minutes, filtered off and dried, giving paroxetine hydrochloride anhydrate (m.p. 118°C).

Example 2

(-)Trans-4-(4'-fluorophenyl)-3-(3'4'-methylenedioxy-phenoxymethyl)piperidine hydrochloride (Paroxetine hydrochloride) as hemihydrate ($\frac{1}{2}H_2O$)

To a solution of 13.5g Paroxetine free base in toluene(300ml) was added a small excess of either concentrated hydrochloric acid(5.2ml)or dilute hydrochloric acid (150mls of 0.35N)

Paroxetine hydrochloride seed was added and the slurry stirred at ambient temperature for 2 hours. The product was washed with toluene/water(25ml 1:1 mixture) and dried at 50°C to give paroxetine hydrochloride as the hemihydrate ($\frac{1}{2}H_2O$) containing 2.5% H_2O with m.p. 128 - 133°C, and IR consistent with authentic material

Example 3

(-)Trans-4-(4'-fluorophenyl)-3-(3'4'-methylenedioxy-phenoxymethyl)piperidine hydrochloride (Paroxetine hydrochloride) as hemihydrate ($\frac{1}{2}H_2O$)

To a solution of paroxetine free base [23.5g] in toluene (ca.500ml) was added 300ml water. Acetic acid was added (6.4g) and after 15 minutes stirring the lower aqueous layer containing paroxetine acetate was separated.

The aqueous layer was clarified by filtration through celite. Concentrated hydrochloric acid (15.0ml) was then added at ambient tempatures in the presence of paroxetine hydrochloride seed and the precipitated product stirred for 1 hour at ambient and then 2 hours at 0-5°C.

The product was filtered, washed with water (2x40ml)and dried at 50°C to give paroxetine hemihydrate containing 2.6% H_2O and consistent IR.

Example 4

Recrystallisation of Paroxetine hydrochloride to give the hemihydrate

(a) 0.50g Paroxetine hydrochloride was recrystallised from 2.5ml IMS (industrial methylated spirit) by dissolving at ca 60 - 70°C and cooling slowly to 20°C then to 5°C. Crystals of paroxetine hydrochloride hemihydrate were deposited and isolated in the normal way.

(b) 0.75gm Paroxetine hydrochloride was recrystallised from 5.0ml water by dissolving at ca. 70°C and cooling slowly to 20°C. Crystals of paroxetine hydrochloride hemihydrate were deposited and isolated in the normal way.

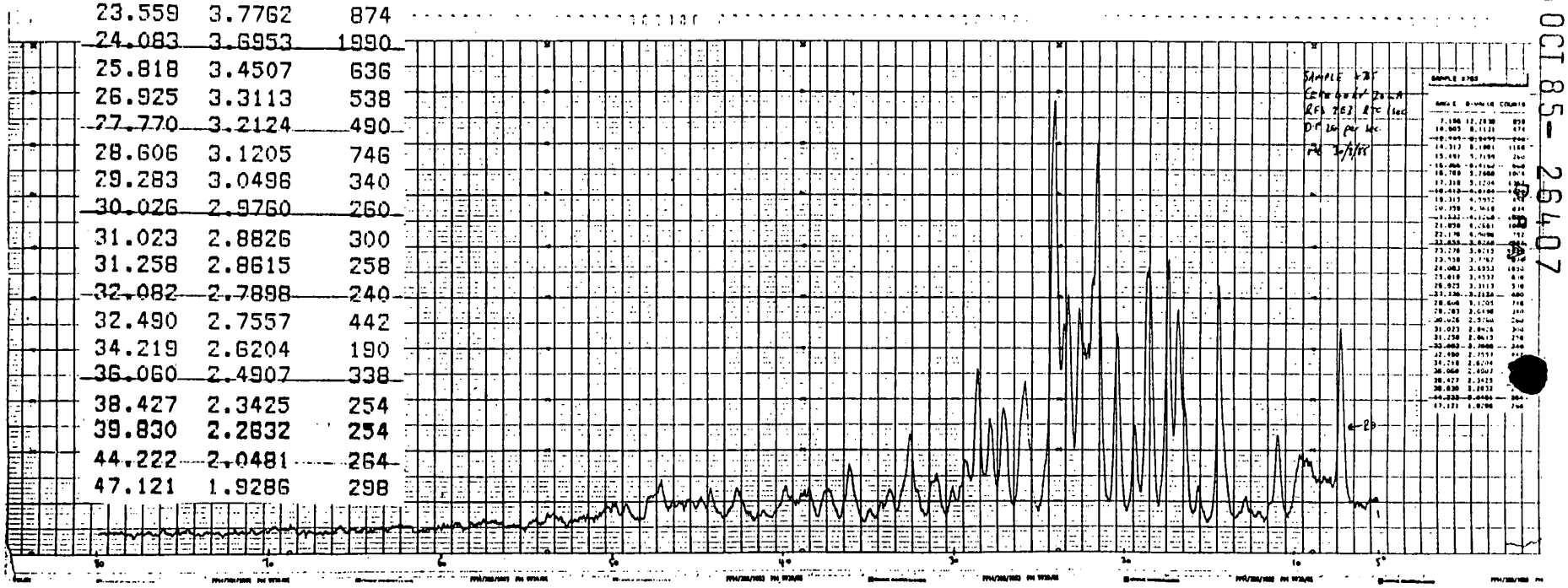
Example 5

Paroxetine hydrochloride isopropanol solvate

8.55g Paroxetine hydrochloride was recrystallised from 50ml isopropanol by dissolving near to reflux, filtering through celite to remove any insoluble solids and allowing to cool to 20°C overnight. The solid product was isolated and dried at 20°C under vacuo overnight to give 6.75g paroxetine hydrochloride as a mono isopropanol solvate containing 13.8% isopropanol, m.p. 98 - 101°C. The solvate of solution was airly weakly bound and could be removed by drying at high temperatures.

ANGLE	D-VALUE	COUNTS
7.196	12.2838	956
10.905	8.1131	474
12.745	6.9453	240
14.313	6.1881	1166
15.491	5.7199	260
16.366	5.4162	568
16.769	5.2868	1004
17.318	5.1204	1362
18.413	4.8184	1120
19.315	4.5952	454
20.359	4.3619	694
21.532	4.1268	1626
21.858	4.0661	1006
22.170	4.0096	792
22.655	3.9248	984
23.276	3.8215	1028
23.559	3.7762	874
24.083	3.6953	1990
25.818	3.4507	636
26.925	3.3113	538
27.770	3.2124	490
28.606	3.1205	746
29.283	3.0496	340
30.026	2.9760	260
31.023	2.8826	300
31.258	2.8615	258
32.082	2.7898	240
32.490	2.7557	442
34.219	2.6204	190
36.060	2.4907	338
38.427	2.3425	254
39.830	2.2832	254
44.222	2.0481	264
47.121	1.9286	298

Fig. 1.



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DFA
80
60
40
20
600
800
1000
1200
1400
1600
1800
2000
3000
4000
Fig. 2
NUJOL MULL
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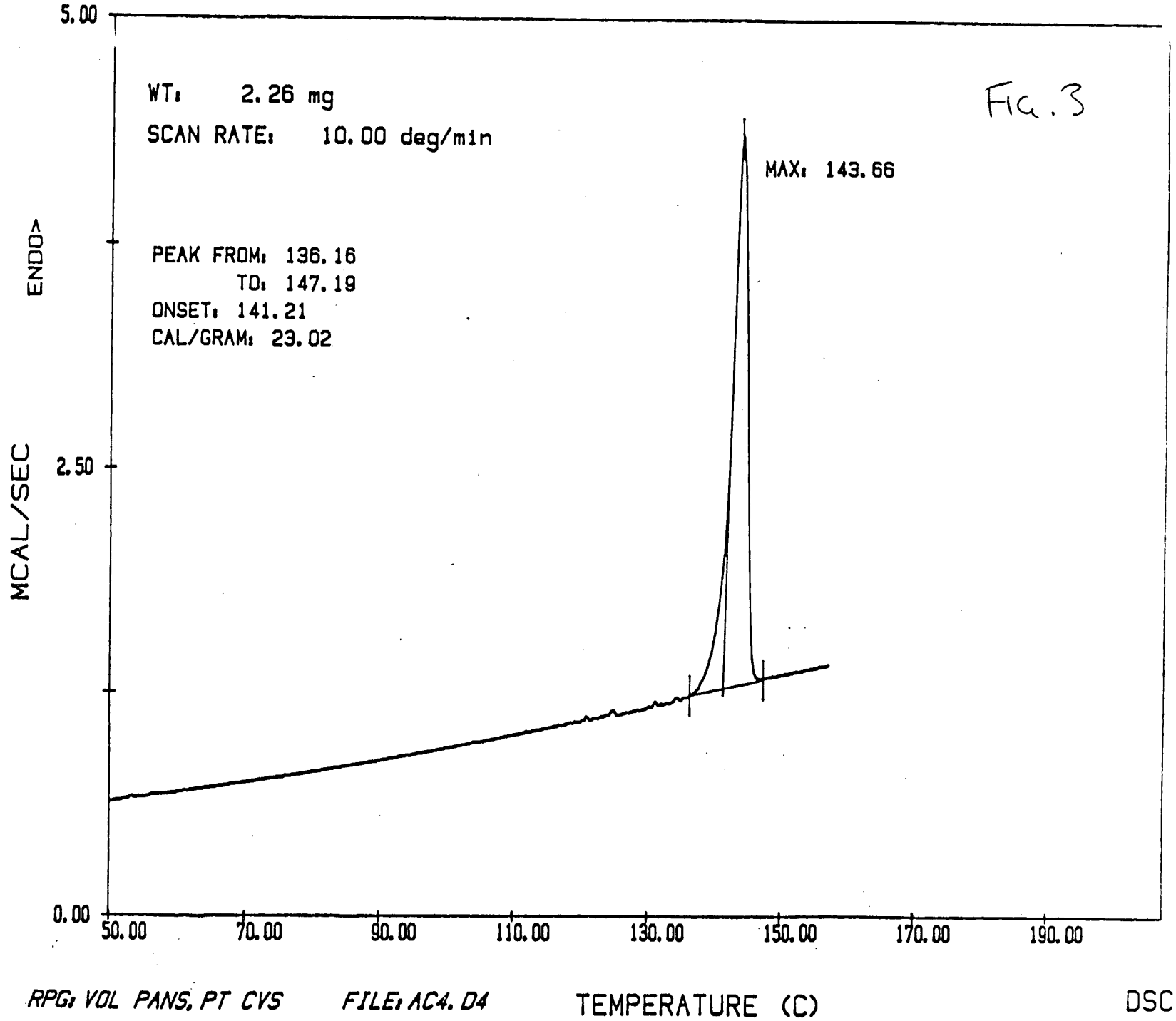

Fig. 3

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Fig. 4.

ANGLE	D-VALUE	COUNTS
6.627	13.3369	256
7.988	11.0684	638
9.466	9.3426	312
11.195	7.9036	318
13.055	6.7811	242
16.446	5.3900	1712
16.896	5.2472	1640
18.620	4.7652	850
19.710	4.5040	842
20.441	4.3447	710
21.884	4.0614	2490
23.875	3.7270	1670
24.664	3.6095	496
25.943	3.4344	512
27.025	3.2992	618
27.445	3.2497	762
28.230	3.1611	740
28.782	3.1017	314
30.035	2.9751	968
30.726	2.9098	446
31.980	2.7985	766
32.877	2.7242	426
33.812	2.6510	278
35.605	2.5214	296
37.182	2.4181	234
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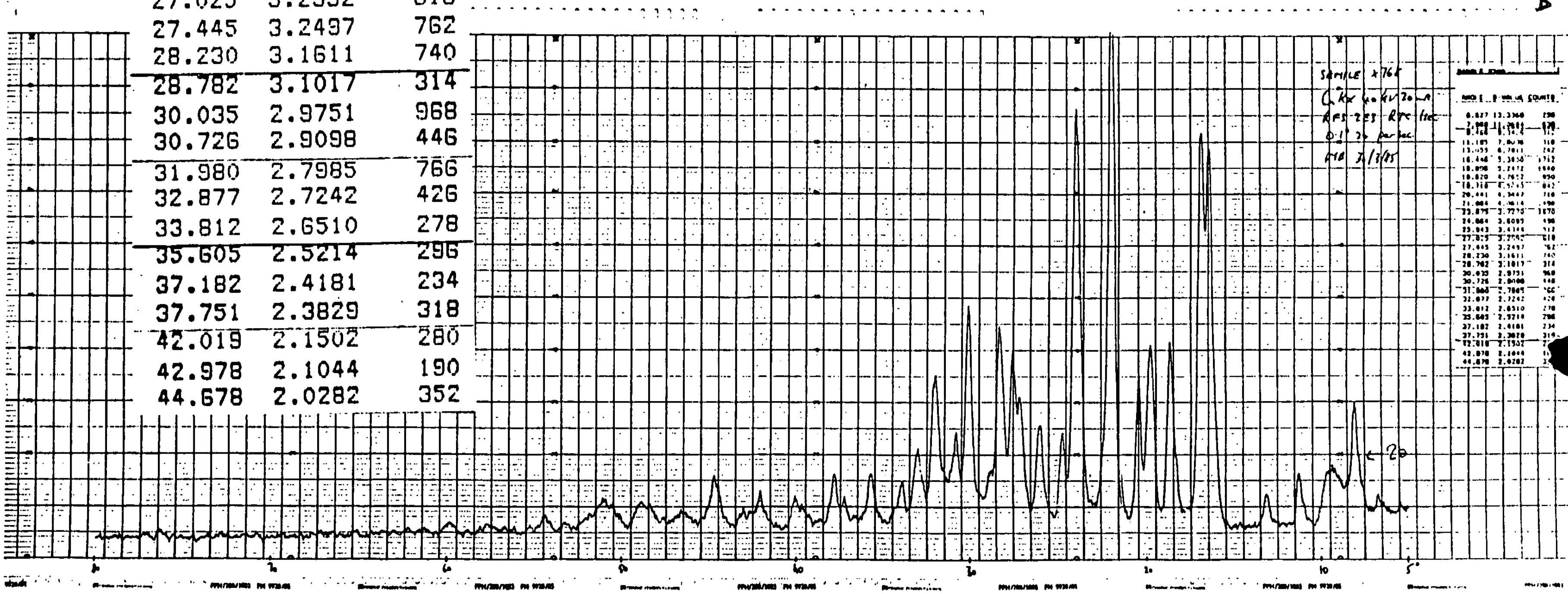

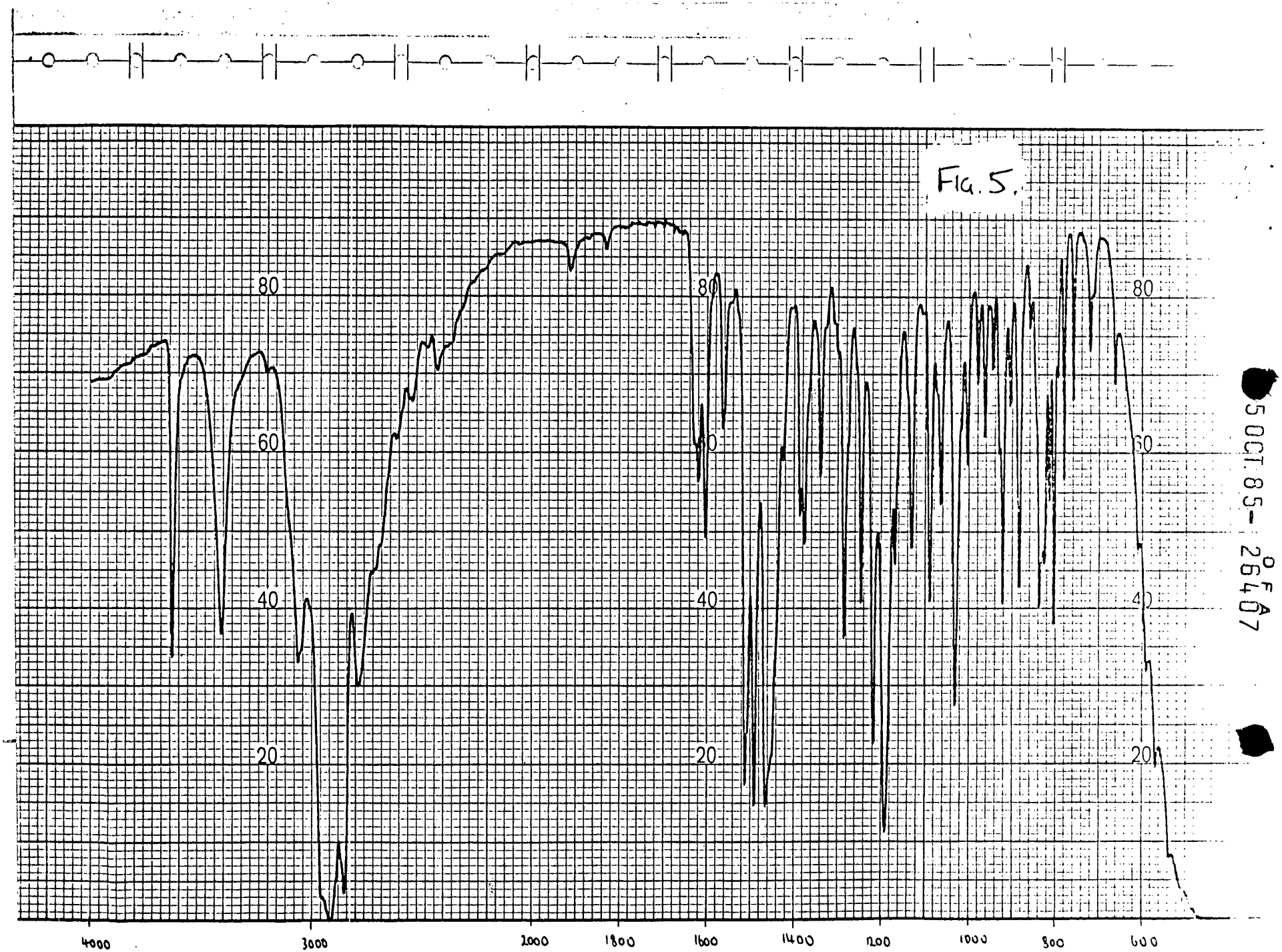
Fig. 5.
80
60
40
20
4000
3000
2000
1800
1600
1400
1200
1000
800
600
NUJOL MULL
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5 OCT. 85- 26407

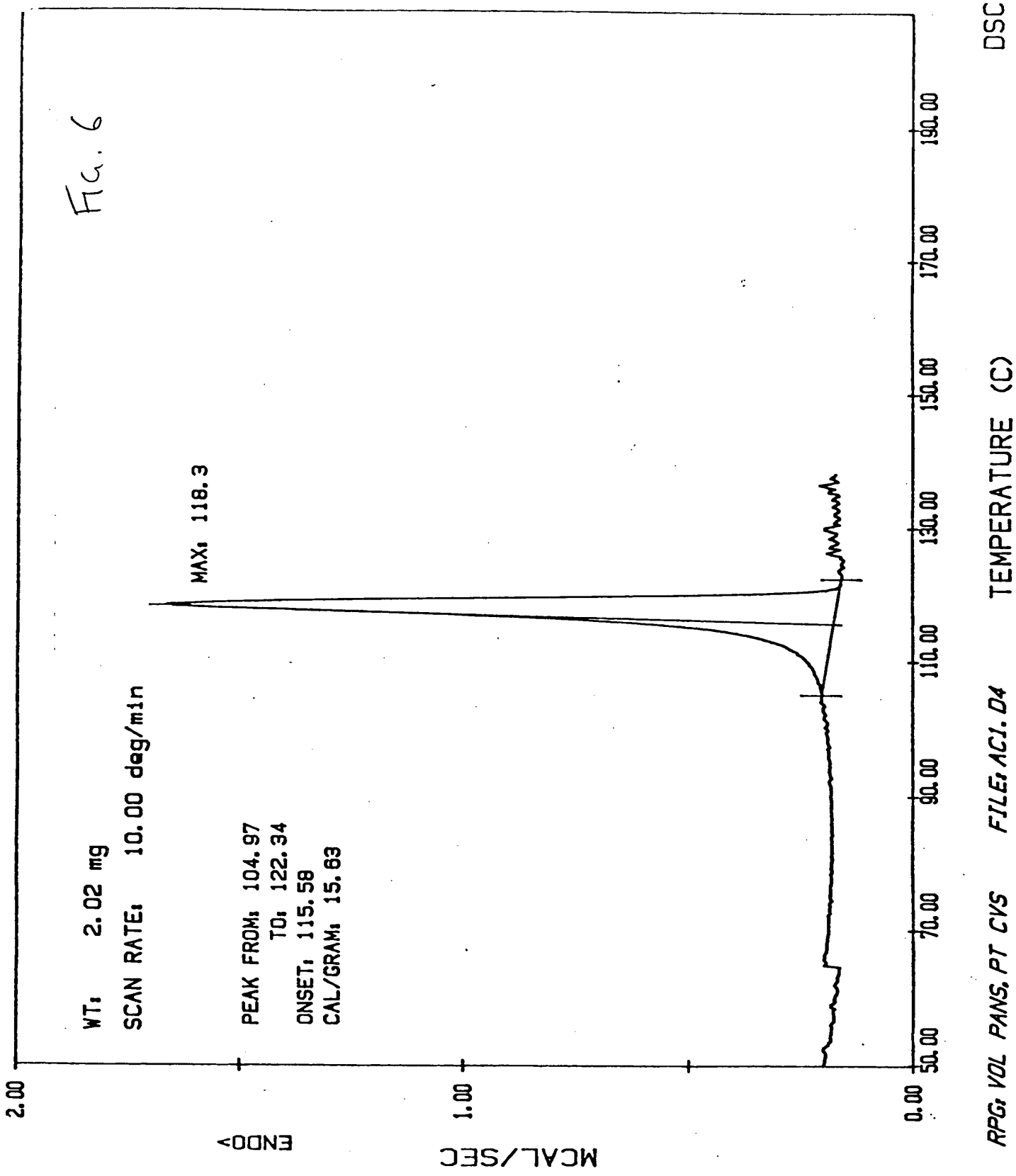
Fig. 6
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PEAK FROM: 104.97
TO: 122.34
ONSET: 115.58
CAL/GRAM: 15.63
2.00
1.00
0.00
ENDO>
MCAL/SEC
50.00
70.00
90.00
110.00
130.00
150.00
170.00
190.00
TEMPERATURE (C)
DSC
RPG: VOL PANS, PT CVS
FILE: AC1.D4